REMARKS

Applicants herein response to the office action mailed October 1, 2002. Applicants have amended claims 20-37 and 40-44 to correct informalities. Upon entry of this amendment, claims 20-46 will remain pending.

The claims are definite

On page 2 of the office action, the examiner made several indefiniteness rejections. Applicants respectfully traverse these rejections.

For definiteness, a claim need only reasonably apprise those skilled in the art of the utilization and scope of the invention. *Hybritech, Inc. v. Monoclonal Antibodies,* 231 USPQ 81, 94-95 (1986). Words are to be given their plain meaning as understood by the person of ordinary skill in the art, particularly given the limitations of the English language. *See* MPEP §§ 707.07(g); 2111.01 (August 2001). Claims are to be given their broadest reasonable interpretation consistent with applicants' specification. *See* MPEP § 2111 (August 2001). In sum, in order to reject the claims on definiteness grounds, it is incumbent on the examiner to show how and why the skilled person having applicants' specification would not be apprised of the invention by the language-at-issue.

Turning first to the term "specific," applicants no longer use it to qualify the term "activity." It is clear from the context of the claims that the activity referred to is that of activated Factor VII.

The examiner also rejected the claims due to the usage of "approximately." Applicants traverse this rejection. The term "approximately" is akin to the term "about," which is considered to be permitted relative terminology. *See* MPEP § 2173.05(b)(A) (August 2001) (concerning "about"). In the context of the claims, the skilled person would realize that the flow rate or pH is generally defined by the recited range in order to suit the particular purpose. Thus, the use of terminology like "approximately" is meant to make the claims expressly recite what the skilled person would understand to be implicit. Under such circumstances, applicants submit that the use of relative terminology is perfectly clear and appropriate, and thus is employed in a manner approved of by MPEP § 2173.05(b). To contend otherwise would impart on the skilled person a rigid absolutism that requires a departure from the sound judgment normally exercised by the skilled person as a matter of law. Applicants therefore request withdrawal of the rejection.

The claimed invention is not taught by the Turecek '620 patent

On pages 3-4, the examiner rejected claims 28-32, 34, 36-39 and 42-46 as anticipated by U.S. Patent No. 6,013,620 to Turecek *et al.* Applicants respectfully traverse this rejection.

Applicants note that in order to reject a claim under 35 USC § 102, the examiner must demonstrate that each and every claim term is contained in a single prior art reference. *See Scripps Clinic & Research Foundation v. Genentech, Inc.*, 18 USPQ2d 1001, 1010 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ

81, 90 (Fed. Cir. 1986); *see also* MPEP § 2131 (August 2001). Claim terms are to be given their plain meaning as understood by the person of ordinary skill in the art, particularly given the limitations of the English language. *See* MPEP §§ 707.07(g); 2111.01 (August 2001). Claims are to be given their broadest reasonable interpretation consistent with applicants' specification. *See In re Zletz*, 13 USPQ2d 1320, 1322 (Fed Cir. 1989) (holding that claims must be interpreted as broadly as their terms reasonably allow); MPEP § 2111 (August 2001).

Not only must the claim terms, as reasonably interpreted, be present, an allegedly anticipatory reference must enable the person of ordinary skill to practice the invention as claimed. Otherwise, the invention cannot be said to have been already within the public's possession, which is required for anticipation. *See Akzo, N.V. v. U.S.I.T.C.*, 1 USPQ2d 1241, 1245 (Fed. Cir. 1986); *In re Brown*, 141 USPQ 245, 249 (CCPA 1964).

The Turecek '620 patent concerns the preparation of compositions containing activated factor VII (factor VIIa). Note the titles of the Examples. Applicants' present invention, on the other hand, seeks to minimize the presence of factor VIIa through the recitation of no more than approximately 5% factor VIIa. Accordingly, the present invention and that of the Turecek '620 patent are different in that the Turecek '620 patent seeks provide factor VIIa whereas the present invention avoids factor VIIa. Applicants therefore submit that the Turecek '620 patent does not anticipate the claims, and therefore the rejection should be withdrawn.

The claimed invention is not suggested by the prior art

On pages 4-7, the examiner rejected claims 20-27 as being obvious over the Sigma Chemical Catalog in view of the Thomas '591 patent, Broze paper, the Berkner '944 patent, the Thomas '321 patent, the Turecek '968 patent and the Scopes paper. The Sigma catalog and the Thomas '591 patent were cited for disclosing the use of the inhibitor benzamidine in purifying factor VII. Broze was cited for disclosing the purification of factor VII without the presence of factor VIIa. The Berkner '944 patent and Turecek '968 patent were cited for methods of removing pathogens from blood products. Thomas was for disclosing the combination of factor VII with factors IX and X. Scopes was cited for disclosing the use of glycerol as a stabilizer. Applicants respectfully traverse this rejection.

On pages 7-9 of the office action, the examiner rejected claims 28-39 and 42-44 as obvious over the Turecek '620 patent in view of the Jorgensen '914 patent in view of the Goldfarb paper and the Scopes paper. The Turecek '620 patent was applied as before. The Jorgensen '914 patent was cited for disclosing the purification of factor VII from recombinant cells using anion exchange. Goldfarb was cited for disclosing protein purification using hydrogels. Scopes was cited for disclosing general protein purification protocols. Applicants respectfully traverse this rejection.

At the outset, applicants note that the examiner must show all of the recited claim elements in the combination of references that make up the rejection. When combining references to make out a *prima facie* case of obviousness, the examiner is obliged to show by citation to specific evidence in the cited references that (i) there was

a suggestion/motivation to make the combination and (ii) there was a reasonable expectation that the combination would succeed. Both the suggestion/motivation and reasonable expectation must be found within the prior art, and not be gleaned from applicants' disclosure. *In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991); *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988); *W.L. Gore v. Garlock, Inc.*, 220 USPQ 303, 312-13 (Fed. Cir. 1983) (holding that is improper in combining references to hold against the inventor what is taught in the inventor's application); *see also* MPEP §§ 2142-43 (August 2001). Thus, the examiner must provide evidentiary support based upon the contents of the prior art to support all facets of the rejection, rather than just setting forth conclusory statements, subjective beliefs or unknown authority. *See In re Lee*, 277 F.3d 1338, 1343-44 (Fed. Cir. 2002).

When an examiner alleges a *prima facie* case of obviousness, such an allegation can be overcome by showing that (i) there are elements not contained in the references or within the general skill in the art, (ii) the combination is improper (for example, there is a teaching away or no reasonable expectation of success) and/or (iii) objective indicia of patentability exist (for example, unexpected results). *See U.S. v. Adams*, 383 U.S. 39, 51-52 (1966); *Gillette Co. v. S.C. Johnson & Son, Inc.*, 16 USPQ2d 1923, 1927 (Fed. Cir. 1990); *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve*, 230 USPQ 416, 419-20 (Fed. Cir. 1986). Applicants address the rejections with these concepts in mind.

The first rejection is overcome by a review of the Sigma catalog and Broze. The Sigma catalog avoids the activation of factor VII by using the powerful protease inhibitor benzamidine. Without the use of benzamidine, conventional anion exchangers used for

purification would activate factor VII to form factor VIIa. Benzamidine, however, is toxic and is a contaminant that cannot be removed completely. Thus, factor VII preparations today that contain benzamidine would not be acceptable to medicinal uses. In contrast, applicants' invention avoids factor VII activation without the use of benzamidine, and thus provides pharmacological factor VII preparations that meet today's standards. See applicants' specification at page 4, lines 4-5 and 15-18.

Broze teaches the use of two QAE-columns at very slow flow rates (0.005 and 0.006 column volumes per minute). Without the presence of benzamidine, these slow rates will result in the activation of factor VII. Accordingly, Broze teaches the use of benzamidine. See page 1243, bottom of column 1.

In contrast, applicants' invention allows for fast flow rates (see passage bridging pages 11-12) in the absence of inhibitors, thereby providing for the first time factor VII with a low presence of factor VIIa with the absence of inhibitors. This is not provided by the combination of references, as explained above. Accordingly, the combination of references do not suggest the claimed invention or provide the skilled person with a reasonable expectation that the invention could be attained. Rather, these references actually teach away from the attainment of a pharmaceutical preparation, and thus destroy an alleged *prima facie* case. *See Ecolochem, Inc. v. Southern California Edison Co.*, 227 F.3d 1361, 1372-75 (Fed. Cir. 2000) (reasoning that prior art references cannot contain a motivation to combine to when one of the references teaches away from the combination). In view of the foregoing, applicants respectfully request withdrawal of the rejection.

The second obviousness rejection is overcome for the same reasons as the anticipation rejection, namely that the Turecek '620 patent concerns the production of factor VIIa preparations, whereas the presence invention produces factor VII while minimizing the production of factor VIIa. The secondary references cannot alter this difference. Additionally, the procedures of the prior art, such as Jorgensen's anion exchangers, would only result in the activation of factor VII. Accordingly, this rejection too should be withdrawn.

Request

Applicants submit that the claims are in condition for allowance, and respectfully request favorable consideration to that effect. The examiner is invited to contact the undersigned at (202) 912-2000 should there be any questions.

Respectfully submitted,

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Marked-Up Copy of Amended Claims

20. (Amended) A stable **[blood coagulation factor]** **pharmaceutical** preparation comprising:

blood coagulation factor VII having a **[specific]** protease activity, when activated, of at least 50 U **[nits(U)]** /mg of total protein, wherein **[in]** said blood coagulation factor preparation is free from blood coagulation inhibitors and contains **[less]** **no more** than approximately 5% of activated blood coagulation factor VII **[(blood coagulation factor VIIa)]**.

21. (Amended) The stable **[blood coagulation factor]** **pharmaceutical** preparation of claim 20, wherein said blood coagulation factor VII has a **[specific]** protease activity, when activated, of greater than 100 Units/mg of total protein.

22. (Amended) The stable **[blood coagulation factor]** **pharmaceutical** preparation of claim 20, wherein said blood coagulation factor VII is present in an amount of between approximately 5 U/mL to approximately 5,000 U/mL.

23. (Amended) The stable **[blood coagulation factor]** **pharmaceutical** preparation of claim 20, wherein said preparation is lyophilized.

24. (Amended) The stable **[blood coagulation factor]** **pharmaceutical** preparation of claim 23, wherein said preparation is stable for at least 12 hours after

reconstitution.

25. (Amended) The stable **[blood coagulation factor]** **pharmaceutical** preparation of claim 20_1 wherein said blood coagulation factor VII is a recombinant protein.

26. (Amended) The stable **[blood coagulation factor]** **pharmaceutical** preparation of claim 20_1 wherein said blood coagulation factor VII is recovered from normal human plasma.

27. (Amended) The stable **[blood coagulation factor]** **pharmaceutical** preparation of claim 26_1 wherein said blood coagulation factor preparation has no detectable transmissible human pathogens.

28. (Amended) A method for preparing a stable **[blood coagulation factor]** **pharmaceutical** preparation comprising:

absorbing blood coagulation factor VII from a biological material onto a chromatographic substrate;

selectively **[eluding]** **eluting** said absorbed blood coagulation factor VII from said chromatographic substrate using a blood coagulation inhibitor-free elution buffer; and

selecting an eluate having a **[specific]** protease activity of at least 50

U/mg of total protein**, when activated, and wherein the pharmaceutical preparation contains no more than approximately 5% activated blood coagulation factor VII**.

29. (Amended) The method for preparing a stable **[blood coagulation factor] pharmaceutical** preparation of claim 28, wherein said elution buffer has a pH of between approximately 5.0 to approximately 9.0.

30. (Amended) The method for preparing a stable **[blood coagulation factor] pharmaceutical** preparation of claim 29, wherein said elution buffer has a pH of between approximately 6.0 to approximately 7.5.

31. (Amended) The method for preparing a stable **[blood coagulation factor] pharmaceutical** preparation of claim **[31] 28**, wherein said chromatographic substrate is an anion exchange material and said selective elution being performed using a chromatography column and a chromatography column flow rate of at least 0.15 column volumes per minute.

32. (Amended) The method for preparing a stable **[blood coagulation factor] pharmaceutical** preparation of claim 31, wherein said flow rate is between approximately 0.17 to 2.0 column volumes per minute.

33. (Amended) The method for preparing a stable **[blood coagulation**

factor] pharmaceutical preparation of claim 28, wherein said chromatographic substrate is an immunoaffinity column specific for factor VII.

34. (Amended) The method for preparing a stable **[blood coagulation factor] pharmaceutical** preparation of claim 28, wherein said chromatographic substrate is a material having hydrophobic groups.

35. (Amended) The method for preparing a stable **[blood coagulation factor] pharmaceutical** preparation of claim 28, wherein said chromatographic substrate is a hydrogel.

36. (Amended) The method for preparing a stable **[blood coagulation factor] pharmaceutical** preparation of claim 28, wherein said biological material is selected from the group consisting of blood, plasma, a plasma fraction, a cell culture and a cell culture fraction.

37. (Amended) The method for preparing a stable **[blood coagulation factor] pharmaceutical** preparation of claim 31, further comprising absorbing said eluate having a **[specific]** protease activity of at least 50 U/mg of total protein onto a second chromatographic substrate having hydrophobic groups and selectively **[eluding] eluting** said absorbed eluate from said chromatographic substrate having hydrophobic groups.

40. (Amended) A stable **[blood coagulation factor]** **pharmaceutical** preparation comprising:

blood coagulation factor VII having a **[specific]** protease activity, when activated, of at least 50 U **[nits (U)]**/mg of total protein, wherein **[in]** said blood coagulation factor preparation is free from blood coagulation inhibitors and contains **[less]** **no more** than approximately 5% of activated blood coagulation factor VII **[(blood coagulation factor VIIa)]**; **and**

at least one additional coagulation factor.

41. (Amended) The stable **[blood coagulation factor]** **pharmaceutical** preparation of claim 40, wherein said **additional** blood coagulation factor is selected from the group consisting of factor II, factor IX and factor X.

42. (Amended) A method for preparing a stable **[blood coagulation factor]** **pharmaceutical** preparation comprising:

absorbing blood coagulation factor VII from a biological material onto an anionic chromatographic column;

selectively **[eluding]** **eluting** said absorbed blood coagulation factor VII from said chromatographic column at a flow rate of between approximately 0.17 to 2.0 column volumes per minute using a blood coagulation inhibitor-free elution buffer having a pH of between approximately 6.0 to 7.5; and

selecting an eluate having a **[specific]** protease activity of at least 50 U/mg of total protein**, when activated, and wherein the pharmaceutical preparation contains no more than approximately 5% activated blood coagulation factor VII**.

43. (Amended) The method for preparing a stable **[blood coagulation factor] pharmaceutical** preparation of claim 42, wherein said biological material is selected from the group consisting of blood, plasma, a plasma fraction, a cell culture and a cell culture fraction.

44. (Amended) The method for preparing a stable **[blood coagulation factor] pharmaceutical** preparation of claim 42, further comprising absorbing said eluate having a **[specific]** protease activity of at least 50 U/mg of total protein onto a second chromatographic substrate having hydrophobic groups and selectively **[eluding] eluting** said absorbed eluate from said chromatographic substrate having hydrophobic groups.